PATENT

DOCKET NO.: ISIS0064-100 (RTS-0175)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventors: **Monia and Watt**

Serial No.: **09/865,993** Group Art Unit: **1635**

Filed: **May 25, 2001** Examiner: **J. Zara**

Title: **Antisense Modulation Of Dual Specific Phosphatase 5 Expression**

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION UNDER 37 CFR §1.132

Sir:

I, C. Frank Bennett, a citizen of the United States, residing at 1347 Cassins Street, Carlsbad, California 92009, do declare and state that:

1 I am the Vice President of Antisense Research at ISIS Pharmaceuticals, Inc., the assignee of the above-identified patent application. I hold the degree of Ph.D., and have been employed by the assignee of this application since 1989. I am an expert in the art of antisense technology.

2. I have read the Office Action dated January 27, 2001 and understand that the claims of this invention have been rejected as allegedly being obvious over the combination of Ishibashi et al., J. Biol. Chem., 1994, 269, 29897-29902, Sato et al., J. Biochem., 1998, 123, 1119-1126, Milner et al., Nature Biotechnol., 1997, 15, 537-541, and U.S. Patent No. 5,801,154. In addition, the statements in the Office Action regarding the alleged reasonable expectation of success by one of skill in the art for inhibiting the expression of dual specific phosphatase 5 with oligomeric compounds are unsupported and incorrect.

3. It is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. It is also not reasonable to expect for any particular gene or mRNA that oligomeric compounds having at least 40% inhibition in the expression will be obtained.

4. For example, as indicated by Exhibits A (inhibition of human tyrosine kinase, non-receptor, 1 mRNA expression in T-24 cells) and B (inhibition of rat urate anion exchanger 1 mRNA expression in Rin-M cells), 80 oligomeric compounds (each being 2'-O-methoxyethyl gapmers) were examined for their ability to inhibit expression (please note that the results are presented as % expression of the control). Referring to Exhibit A, only 3 out of 80 oligomeric compounds inhibited expression by at least 40%. Referring to Exhibit B, only 1 out of 80 oligomeric compounds inhibited expression by at least 40%. This observation is true for a number of genes. It is never possible to predict **before** the appropriate experiment is performed, which oligomeric compounds, if any, will generate the desired level of inhibition of expression.

5. This evidence demonstrates that one skilled in screening of oligomeric compounds cannot, *a priori*, reasonably expect a particular level of inhibition (i.e., such as at least 40%) of a gene or mRNA simply because methods of screening oligomeric compounds are available and/or routine. The statements in the Office Action regarding reasonable expectation of success are neither accurate nor capable of being supported.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5-26-04 By: C. Frank Bennett

C. Frank Bennett, Ph.D.